Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 20, 21, and 24-33 are pending in the application, with claims 20, 21, 24, 26, 27, and 30 being the independent claims. Claims 21, 24-30 and 33 are sought to be amended by the present amendment. Claims 2-5, 7, 9, 10, 12, 14-19, 22, and 23 are sought to be cancelled by the present amendment without prejudice to or disclaimer of the subject matter therein. Claims 1, 6, 8, 11 and 13 were cancelled by previous amendment without prejudice to or disclaimer of the subject matter therein.

Applicants have amended claims 21, 24-30 and 33 to put these claims into better condition for allowance. Specifically, claims 21, 24-26 and 30 have been amended to recite "hepatocellular carcinoma" rather than "diseases of the liver," "liver disease," "cancer," "cancers," or "cancers of the liver." Claims 27 and 28 have been amended to replace "excipients" or "salts" with their singular forms, "excipient" or "salt", respectively. Claim 25, which depends from independent claim 24, has also been amended to replace the article "a" prior to "compound of Formula III" with the article "the" to correctly denote antecedent basis. Lastly, claims 29 and 33 have been amended to correct typographical errors by replacing "mercaptopuririe" with "mercaptopurine" and replacing "nrocarzinostatin" with "neocarzinostatin." Support for these last two amendments can be found in the specification at page 20, lines 19 and 20, and at page 21, lines 6 and 28.

These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

I. Rejections under 35 U.S.C. § 112, First and Second Paragraphs

Claims 2-5, 7, 9-10, 12, 16-19, 21-22, and 24-33 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement and containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. (Office Action, at page 2, lines 9-13.)

To expedite prosecution and without acquiescing to the propriety of the rejection to claims 2-4, Applicants have cancelled claims 2-4, rendering moot this basis for rejection.

The Examiner also states that claims 3-5, 7, 9-10, 12, 16-19, 21-22, and 24-33 are drawn to compositions and methods of use for treating any liver disease, cancer or viral infection, and alleges that "[t]he only liver disease disclosed in the specification is hepatocellular carcinoma. Nothing is disclosed in support of all/or any liver disease, cancer, viral infection or prevention of all cancers of the liver." (Office Action, at page 3, lines 1-4.)

To expedite prosecution and without acquiescing to the propriety of the rejection, Applicants have cancelled claims 3-5, 7, 9-10, 12, 16-19, and 22, rendering moot this basis for rejection. Applicants have also amended claims 21, 24-26 and 30 to recite

"hepatocellular carcinoma" rather than "diseases of the liver," "liver disease," "cancer," "cancers," or "cancers of the liver."

Applicants assert that claims 21 and 24-33, as presented, are sufficiently described in the specification to clearly convey the information that Applicants have invented the claimed subject matter, thus satisfying the written description requirement for these claims.

Claims 3-5, 7, 9-10, 12, 16-19, 21-22, and 24-33 are also rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for using compound III to treat hepatocellular carcinoma, allegedly does not reasonably provide enablement for using compound III or its prodrugs to treat any liver disease, cancer, viral infection or prevent recurrence of any liver cancer. (Office Action, at page 3, lines 10-14.)

To expedite prosecution and without acquiescing to the propriety of the rejection, Applicants have cancelled claims 3-5, 7, 9-10, 12, 16-19, and 22, rendering moot this basis for rejection. As described above, Applicants have also amended claims 21, 24-26 and 30 to recite "hepatocellular carcinoma" rather than "diseases of the liver," "liver disease," "cancer," "cancers," or "cancers of the liver."

Applicants assert that claims 21 and 24-33, as presented, are fully enabled by the specification, and that the specification would reasonably enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 2-5, 7, 9-10, 12, 16-19, 21-22, and 24-33 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for allegedly failing to particularly point out

and distinctly claim the subject matter which Applicants regard as the invention. (Office Action, at page 6, lines 12-14.) Specifically, the Examiner states that "[f]or the reasons set forth above under 35 USC 112, first paragraph, the claims are indefinite." (Office Action, at page 6, line 15.)

As discussed above, Applicants have cancelled claims 2-5, 7, 9-10, 12, 16-19, and 22, rendering moot this basis for rejection. Applicants have also amended claims 21, 24-26 and 30 as described above under the 35 U.S.C. 112, first paragraph, rejection of the claims.

Applicants believe that the rejections of claims 2-5, 7, 9-10, 12, 16-19, 21-22, and 24-33 under 35 U.S.C. §112, first and second paragraphs, have been overcome and respectfully request that the Examiner reconsider and withdraw these rejections.

II. Double Patenting Rejection

Claims 2-5, 7, 9-10, 12, and 14-33 are rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 34, 53-60, 95-145, and 147-172 of U.S. Patent No. 6,312,662, Erion *et al.* ("the '622 patent") (Office Action, at page 7, lines 12-14.) Applicants respectfully traverse this rejection.

The Examiner contends that while these allegedly conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims allegedly are drawn to the same subject matter, and because the invention of the pending application is within the claims of the '622 patent. (Office Action, at page 7, lines 14-16.) The Examiner states that "[i]n some of the compounds of US '662, Z, W, W' are not

H at the same time, some of them must be alkyl, while in the instant application, V, Z, W, W' are all H. However, H and alkyl are art recognized equivalents." (Office Action, at page 7, lines 16-19.) The Examiner concludes that "one of ordinary skill in the art would have known that H and alkyl are equivalents." (Office Action, at page 8, lines 2-3.)

As discussed above, claims 2-5, 7, 9-10, 12, 16-19, 22 and 23 have been cancelled, rendering moot this basis for rejection. Applicants submit that remaining claims 20, 21, and 24-33 are not obvious in light of claims 34, 53-60, 95-145, and 147-172 of the '662 patent, and that the pending claims of the current application are patentably distinct from the claims of the '622 patent.

An obviousness-type double patenting rejection is analogous to a failure to meet the nonobviousness requirement of 35 U.S.C. § 103. Accordingly, analysis of an obviousness-type double patenting rejection should follow the guidelines used for analysis of a 35 U.S.C. § 103 obviousness determination. *See* § 804 of the Manual of Patent Examining Procedure (MPEP), 8th ed. (August 2005), at pp. 800-21 to 800-26, especially p. 800-21.

The claims of the pending application are drawn to specific S, *cis* isomers of cytarabine-4-pyridyl prodrugs, to pharmaceutical compositions of the S, *cis* prodrug isomers, and to methods of treatment using the S, *cis* prodrug isomers. The '662 patent and its claims fail to teach or suggest the specific S, *cis* configuration of the cytarabine-4-pyridyl prodrugs of Applicants' claims.

The Examiner argues that both the pending claims and the claims of the '662 patent are drawn to the same subject matter, and that the invention of the pending

application is within the claims of the '622 patent. (Office Action, at page 7, lines 15-16.)

However, the fact that a claimed species is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness. *In re Baird*, 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994). Absent a suggestion to make and use the specific S, *cis* isomers of Applicants' claims, no *prima facie* case of obviousness has been established.

Moreover, domination (of the claims of a patent over claims of another patent or application), by itself, *i.e.*, in the absence of statutory or nonstatutory double patenting grounds, cannot support a double patenting rejection. *In re Kaplan*, 789 F.2d 1574, 1577-1578 (Fed. Cir. 1986). *See also* § 804, MPEP, 8th ed. (August 2005), at p. 800-19.

Even assuming *arguendo* that a *prima facie* case of obviousness has been established based on the '662 patent claims, Applicants submit that the unexpectedly better activation of the claimed S *cis* isomer to give araCMP by human liver microsomes compared to the diastereomeric isomer would overcome any basis for *prima facie* obviousness, and thus obviousness-type double patenting, that the Examiner may assert.

Applicants respectfully direct the attention of the examiner to the Biological Examples beginning on page 69 of the specification. Example A presents the results of experiments in which the activation of Compound A and Compound B, two cytarabine-4-pyridyl prodrugs, to araCMP by human liver microsomes was measured. Compound A is a 2R,4S isomer (an S, *cis* isomer, or a compound of Formula III) while compound B is a 2R,4R isomer (an R, *cis* isomer) (see page 68, line 24, to page 69, line 4). As reported on page 72, Compound A is activated at a 2.6-fold greater rate compared to

Compound B. As reported on page 74, Compound A produced significantly higher araCTP levels in the liver than Compound B at all but the 4-hour time-point.

Such increased activation in the liver and the resultant increased tissue concentration is of great practical consequence. As discussed on page 1 of the specification, use of araC to treat hepatocellular carcinoma is characterized by dose limiting toxicity in organs of toxicity (e.g. bone marrow). By increasing activation in the liver, one can improve the effectiveness of araC in the liver by specifically delivering higher concentrations of araCTP to CYP3A4-expressing liver cells. This unexpected result is not taught or suggested by the '662 patent.

Applicants thus submit that '622 patent provides no suggestion to make or use the S, *cis* prodrug isomers of pending claims 20, 21, and 24-33, and that the compounds claimed in the '662 patent, and those in pending claims 20, 21, and 24-33, are patentably distinct from one another.

Applicants believe that the rejection of claims 2-5, 7, 9-10, 12, and 14-33 under the judicially created doctrine of obviousness-type double patenting has been overcome and respectfully request that the Examiner reconsider and withdraw the rejection.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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